UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: EPHEDRA PRODUCTS LIABILITY LITIGATION	:	04 MD 1598 (JSR)

AFFIDAVIT OF DAVID B. ALLISON, Ph.D.

I, David B. Allison, Ph.D., after first being duly sworn upon oath do depose and state the following:

1. Attached as Exhibit A is a true and correct copy of an expert report memorializing my expert opinions given in *In re Ephedra Products Liability Litigation*, MDL-1598, pending in the United States District Court for the Southern District of New York before the Honorable Jed S. Rakoff.

2. The contents of the expert report, attached as Exhibit A, embody the opinions I hold in this matter, and are accurate as of today. I hereby incorporate the attached report as if fully rewritten here.

3. I have personal knowledge of all matters set forth in this affidavit and the attached expert report, and I would be competent and willing to testify at trial regarding both.

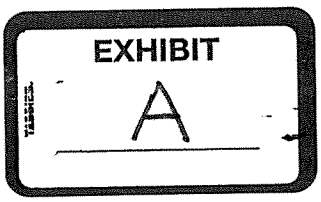
FURTHER AFFIANT SAYETH NAUGHT.

SWORN TO BEFORE ME and subscribed in my presence and subscribed on this 30 day of November 2004 by Mary Ann B. Rice.

EXPERT REPORT OF David B. Allison, Ph.D.

A. Background and Qualifications.

1. I have been retained by Ulmer and Berne, LLP, to render expert scientific opinions in the matter of multidistrict litigation concerning ephedra-containing products.
2. I am Professor (with tenure) of the Department of Biostatistics, Head of the Section on Statistical Genetics, and Director of the National Institutes of Health-funded Clinical Nutrition Research Center at the University of Alabama at Birmingham.
3. I have secondary appointments as a Professor in the Department of Nutrition Sciences; Department of Medicine, Division of Rheumatology, and Department of Genetics at the University of Alabama at Birmingham.
4. I previously served as an Associate Research Scientist at the NIH-funded New York Obesity Research Center at Saint Luke's/Roosevelt Hospital Center and as Associate Professor of Medical Psychology in Psychiatry at Columbia University in New York City.
5. I have extensive experience in the design and implementation of human clinical research studies for dietary and weight-loss products and obesity treatments.
6. I have extensive experience in the study, research, and analysis of obesity, its treatment, and dietary and other weight-loss programs and drugs and their effects on the human body.
7. I received my Ph.D. in Clinical and School Psychology from Hofstra University in Hempstead, New York in July 1990.
8. I completed a Post-Doctoral Fellowship in the Departments of Pediatrics and Behavioral Psychology at Johns Hopkins University School of Medicine in 1991.
9. I completed a three-year National Institutes of Health Post-Doctoral Research Fellowship in the Department of Medicine & Obesity Research Center at the Columbia University College of Physicians and Surgeons and Saint Luke's/Roosevelt Hospital in 1994. This fellowship entailed designing and conducting original research in the area of human obesity.
10. As an Associate Research Scientist for the New York Obesity Research Center, I was primarily involved with designing and conducting original research in human obesity and related areas, collaborating with other investigators on their projects, particularly with respect to data analysis, and training students, interns, and post-doctoral fellows with respect to obesity research projects.
11. Since 1998, I have periodically served as a consultant to the Federal Trade Commission (FTC) on the validity of weight-loss product claims. In that capacity, I have reviewed numerous clinical research studies in order to determine whether product claims are supported by the research.
12. In 2002, I have periodically served as a consultant to the Food and Drug Administration (FDA) on the validity of weight-loss product claims.
13. In 2001, I was retained by the United States Postal Inspectors Office to consult on the validity of claims made with respect to commercial weight loss products.



14. In 2002, I served on a special Public Affairs Task Force of the North American Association for the Study of Obesity (NAASO) to provide information regarding dietary supplements for weight loss to the U.S. General Accounting Office (GAO) – 2002.

15. From 1996-1997, I was a consultant to the Food and Drug Administration in their oversight and collaborative development of Proctor & Gamble's post-market surveillance of olestra (Olean).

16. From 1996-1999, I served as a member of an expert advisory panel convened by the Life Sciences Research Office of the Federation of American Societies of Experimental Biology at the behest of the Food and Drug Administration to prepare a document advising the FDA as to how to review petitions for new food additives.

17. Since 1996, I have also acted in the capacity as consultant for major pharmaceutical companies to design and implement clinical studies including but not limited to studies testing weight-loss medications or products.

18. I have authored, in whole or in part, over 200 articles appearing in peer-reviewed publications. Many of these articles address nutrition, obesity and weight-loss programs, treatment, medications, study design, and statistical analysis.

19. I have also edited, authored, or co-authored multiple text books and chapters in text books on the topics of nutrition, obesity, and weight-loss.

20. I conduct extensive research on the causes, consequences, and treatment of obesity; on the development and evaluation of statistical methods; and on study design.

21. I teach in and direct an NIH-funded Nationally-attended short course on statistical genetic methods for obesity and nutrition researchers.

22. I have played a major role in the design, analysis, and interpretation of several clinical trials involving herbal products and other alternative treatments. These studies include two randomized clinical trials of products including ephedrine.

23. My experience, training, and research expertise qualifies me to offer informed opinions on the evidential basis or lack thereof for claims that ingestion of products containing ephedra alkaloids cause particular outcomes.

24. My curriculum vita is attached as Exhibit A and this includes a complete listing of my publications during the preceding 10 years.

B. <u>Materials Reviewed and Relied Upon</u>.

1. Attached as Exhibit B is a list of documents I have reviewed to date and which I will be relying on with respect to the opinion contained in this Report. To insure that, to the greatest extent possible, I reviewed all relevant literature, I have relied on materials that I have identified via thorough, regular, and up-to-date searches of electronic databases including, but not limited to Medline and Science Citation Index. In addition to the specific items listed in Exhibit B, I have reviewed many other documents involving ephedra and ephedrine and also draw on my general fund of knowledge from years of study and reading in the areas of obesity, statistical methods, and scientific methods. For example, with respect to clinical trials, the reports by Shekelle et al. (2003) and Allison et al. (2001) reference multiple clinical trial reports and I have read most or all of those

reports. Finally, I have reviewed the plaintiffs' expert reports.

2. I reserve the right to supplement and/or modify my report and opinions as new and/or additional information is presented or obtained or analyses are completed, including but not limited to deposition transcripts of plaintiffs' experts, documents products by plaintiffs' experts, amended pleadings or new analyses such as rebuttal reports provided by Plaintiffs or their experts.

C. Prior Testimony.

1. Attached as Exhibit C is a list of all other cases in which I have testified as an expert witness at trial or in deposition in the last four years.

D. Compensation.

1. Attached as Exhibit D is a description of my compensation for the work done on this case.

E. Opinions and Bases

1. The opinions in this report are based upon my experience, training, and research expertise (including those things listed in Exhibit A), the material identified in this report, and the materials listed in Exhibit B.

2. I will address the following issues

2.1. What does and does not constitute competent and reliable scientific evidence for claiming that a product causes a particular outcome.

2.2. The risks of obesity and overweight.

2.3. The benefits of weight loss among overweight and obese persons.

2.4. The efficacy of ephedra and ephedrine containing products for weight loss.

2.5. The extent to which there is or is not competent and reliable scientific evidence that ephedra or ephedrine cause or increase the risk of:

(a) ischemic stroke;
(b) hemorrhagic stroke;
(c) seizures;
(d) cardiac injury;
(e) psychotic injury;
(f) primary pulmonary hypertension (PPH);
(g) heat-related injuries.

2.6. Rebuttal of plaintiffs' expert reports.

3. **What does and does not constitute competent and reliable scientific evidence for claiming that a product causes a particular outcome?**

3.1. Standards of Evidence.

3.1.1. Before proceeding to an evaluation of relevant evidence, it is important to clarify the standard of evidence. I refer to scientific evidence and by evidence I mean facts that could potentially lead to a reasonable *conclusion* that causation exists as opposed to facts that could lead one to *conjecture* or *hypothesize* about putative causation. Clearly, this standard requires that we seek evidence

generated using procedures generally accepted in the scientific community as capable of supporting valid conclusions as to causation.

3.1.2. When evaluating outcome claims about effects of products in humans, there are clear standards accepted by the biomedical research community. These standards are articulated in a number of publications relating to testing effects of interventions in general (e.g., Meinert et al., 1986), interventions for weight control (Allison et al., 1997; Committee for Proprietary Medicinal Products, 1997; FDA, 1996; Gadbury et al., 2003; Anderson et al., 1998), dietary supplements in particular (Swanson et al., 2002; Goldman, 2001; Allison et al., 2001), and in the legal context specifically (Green et al., 2000). Although there may be nuances to studying effects with one type of intervention (product, program, substance) as compared to another, the same general principles of sound experimental design, statistical analysis, and interpretation apply.

3.1.3. As an aside, I note that the Federal Trade Commission uses language very similar to this. Their standard of evidence (e.g., see http://www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm), is "Competent and Reliable Scientific Evidence." The FTC typically requires claims about the efficacy or safety of dietary supplements to be supported with "competent and reliable scientific evidence," defined in FTC cases as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."

3.1.4. A key point in the preceding paragraph is the joint concept of objectivity and observability in the scientific process. The process leading to conclusions should be an objective one that is articulatable and observable and, therefore, can be checked and reproduced by other scientists as well as evaluated for validity. To illustrate this point, consider the fact that many scientific journals, including the prestigious *Proceedings of the National Academy of Sciences*, ask their peer-reviewers to answer the following question when evaluating manuscripts that have been submitted for publication "Are the procedures described sufficiently well that the work can be repeated?" Simply stating that one has reviewed evidence and come to a conclusion without describing what the *objective* criteria for reaching such a conclusion are and showing that those criteria were met does not make something a valid scientific opinion.

3.2. Types of Information that are Not Generally Accepted by the Scientific Community as Sufficient Evidence that a Product Causes an Effect.

Several types of data may support *conjecture*, but cannot support *conclusions* with respect to any effects or lack thereof in humans.

3.2.1. Extrapolation from the effects of one substance to another. Two or more substances may have some similarities with respect to chemical composition, molecular structure, selected physiological responses, traditional classifications, or patterns of use. In such situations, one may be inveigled to conclude that effects demonstrated to be produced by one of the substances is therefore also produced by the other substances that share one or more similarities. But, again, such 'chemical analogies' can only support conjecture and not conclusions. There are numerous examples of substances that are quite similar in many ways and yet have markedly different effects in other ways. For example, both olanzapine and ziprasidone are drugs used to treat people with various psychiatric conditions and are classified as *antipsychotics*. Both are antagonists of the

5HT2c (serotonin) receptor and, because of this, both could be predicted (conjectured) to promote weight gain (Allison & Casey, 2001). Yet, for reasons that are not fully understood, olanzapine causes substantial weight gain in humans and ziprasidone does not (Allison et al., 1999). Similarly, sibutramine is an anorexigen that reduces appetite and body weight in humans. It is a combined serotonin and norepinephrine reuptake inhibitor and, therefore, very similar to a number of other drugs that are classified, marketed, and effective as antidepressants. Because of this, sibutramine was initially developed and evaluated as a potential antidepressant (James, 2004). However, for reasons that are not fully understood, sibutramine was not found to be effective as an antidepressant in the early pharmaceutical trials but did produce weight loss. It was therefore switched from a potential antidepressant to a potential anorexigen and eventually brought to market as such. As these examples illustrate, we cannot conclude that one substance will produce similar effects to those produced by other substances, but can only use these other similarities as a basis for speculation and hypothesis generation.

3.2.2. Extrapolation from effects observed in one species to another. There are clear benefits to studying putative effects of substances in animal models when it is excessively difficult, unethical, or impossible to study such substances in humans. Such studies may help us understand basic physiology and provide information about what the effects are in one species and, thereby, support conjecture about what the effects might be in other species. However, these conjectures are always based on extrapolations that contain inherent uncertainty (Ruelius, 1987; Clewell & Andersen, 1985; Crouch, 1983; Dixon, 1976).

There are numerous examples of substances that have markedly different effects in one species than another and such differences are often not predictable based on known physiology. For example, leptin is a potent anorexigen and promoter of weight and fat loss in every mammalian model organism studied including mice, rats, and dogs (Mantzoros, 1999) and, on this basis, Amgen conjectured that it would be effective in promoting weight loss in humans and spent many millions of dollars to investigate this. Unfortunately, in humans, administration of exogenous leptin has, at best, trivial effects on weight and fat loss in humans (Heymsfield et al., 1999) and Amgen has abandoned it as a potential treatment for ordinary obesity (See: *http://www.hhmi.org/bulletin/pdf/mar2003/Leptin.pdf*).

Many other examples of cross-species differences in responses to substances can be cited. In fact, as the plaintiffs' experts point out, it is even possible that within the human species, a substance may have markedly different effects in some individuals relative to others due to genetic differences among individuals. If within-species genetic differences can have such profound moderating effects, then surely different species, which are far more genetically different than are different individuals within a species, can respond differently to the same substance. For these reasons, extrapolations from one species to another remain a basis for conjecture and not a basis for conclusions.

3.2.3. Extrapolation from *in vitro* studies. In vitro studies typically involve isolated cells or tissue biopsies studied 'in glass'. Again, these can be of great value in understanding cellular physiology or biochemical reactions. However, as Goldstein & Henifin (2000) note, "quantitative determinations of human toxicity based on in vitro studies usually are not considered appropriate." This is because we cannot be sure that what occurs in cells or tissues outside the body is what will occur in whole living organisms. Lin (1998) points out "The difficulty in extrapolation lies in the many intrinsic differences between animals and humans, as well as the complexity of the whole body, with a great number of interdependent factors." Indeed, Goldstein & Henifin (2000) define

extrapolation as "The process of estimating unknown values from known values" making clear that the values produced by such a process are only projections and not observations.

3.2.4. Inference from anecdotes. Case reports are anecdotes that can alert physicians, regulators, and other interested parties about a *plausible* connection between exposure to a stimulus and experiencing some event. That is, they can support hypothesis generation and, depending on the risks and benefits involved and the subjective threshold for action on the part of the party considering them, may even merit prudential action. However, not only are case reports incapable of demonstrating causation, they are not even capable of demonstrating association (Adams, 2004). This is because events may occur among people exposed to some putative causal agent by mere chance alone. Without a randomized control group, there is no way to unequivocally rule out confounding factors and, thereby, determine causation. Furthermore, without a properly sampled group of exposed and unexposed subjects to compare (as in a cohort study) or a properly sampled group of subjects that experienced or did not experience the event of interest (as in a case-control study), one cannot assess whether there is an association (as defined in section 3.3.3 below) between exposure and outcome. One can attempt in case reports to rule out other competing explanations for an individual experiencing an event. However, even when this is done in a thorough and unbiased way by a qualified expert, it must be acknowledged that knowledge is limited and simply because we cannot identify the alternative cause of an event does not mean one does not exist. Thus, as Shekelle (2003) pointed out in his report "Classification as a sentinel event[1] does not imply a proven cause and effect relationship."

3.2.5. Extrapolating from effects on putative mediating variables. It is tempting to conclude that if substance X is known or believed to cause physiologic response Z and physiologic response Z is known or believed to cause outcome Y, then exposure to substance X must cause outcome Y. However, this disregards the very real possibility that the ability of Z to cause Y may depend on the context. Therefore, even if the postulated causal links X → Z and Z → Y (I use the notation 'A → B' to denote 'A causes B') have been separately demonstrated, X → Y may not be true because X may also cause other physiological responses, W, and W may have effects on Y that cancel out those of Z. The human body has many complex feedback systems and therefore, although X → Z and Z → Y may have been separately demonstrated, it is still necessary to demonstrate directly that X → Y before the proposition can be accepted. Moreover, often we believe that Z → Y but, because physiological responses can generally not be assigned to subjects at random, we usually really know that Z is associated with Y and do not know for certain that manipulations of Z by an outside force will produce the hypothesized effect on Y. That is why, for example, despite the fact that it is known that certain drugs lower certain serum lipids and it is also known that these serum lipids are *associated* with increased risk of heart disease, it was necessary to conduct randomized trials showing that these drugs actually reduced the rate of new onset heart disease in people (Strandberg et al., 2004).

Examples exist of situations where a hypothesized causal sequence from X to Y have not held up despite strong evidence and/or belief that X → Z and that Z → Y. For example, it is clear that certain drugs, labeled antiarrhythmic agents (i.e., X), reduce arrhythmias (i.e., Z) and it is also

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1 In Shekelle's terminology, a sentinel event was one in which an adverse event was experienced and there was "documentation that the subject had consumed ephedra within 24 hours prior to the adverse event, or a toxicological examination revealing ephedrine or one of its associated products in the blood or urine. We also sought evidence that an adequate investigation had assessed and excluded other potential causes. Cases that met all these criteria were labeled 'sentinel events.'"

believed that arrhythmias increase risk of serious cardiac events and death (i.e., Y) as pointed out by plaintiffs' experts. Therefore, it is reasonable to conjecture that antiarrhythmic agents will reduce risk of death among patients experiencing arrhythmias. However testing this conjecture requires collection of additional data and two famous trials referred to as the CAST and CAST-II studies were conducted to test the effects of three antiarrhythmic agents (encainide, flecainide, and moricizine). Completely contrary to the well-informed and well-intentioned expectations of experts in the field, "CAST-II was stopped early because the first 14-day period of treatment with moricizine after a myocardial infarction was associated with excess mortality ...As with the antiarrhythmic agents used in CAST-I (flecainide and encainide), the use of moricizine in CAST-II to suppress asymptomatic or mildly symptomatic ventricular premature depolarizations to try to reduce mortality after myocardial infarction is not only ineffective but also harmful" (Anonymous, 1992). This shows that our ability to predict effects based on hypothesized causal sequences is limited. Our physiologically-based predictions represent a source of interesting hypotheses, but not a source for drawing conclusions.

3.3. Types of Information that are Generally Accepted by the Scientific Community as Sufficient Evidence that a Product Causes an Effect.

3.3.1. With respect to assessing any possible effects, including putative deleterious effects, if practical and ethical issues were ignored, the ideal source of evidence would be one or more large double-blind randomized placebo controlled trials (RCTs) of the putative cause of interest, on the putative effect of interest, in a sample from the population of interest. Importantly, these RCTS must be well designed, well executed, and well analyzed.

3.3.2. However, one or more RCTs finding supportive results are not sufficient to support a claim if they are only a subset of a larger number of studies some of which obtain contradictory evidence and the weight of evidence is not supportive.

3.3.3. However, for practical or ethical reasons, it is often impossible to conduct an RCT to address a particular question. In such situations, an observational (epidemiologic) study in which one studied people who were exposed (through their own choice or other circumstances) to the substance of interest and compared them to people who were not so exposed might be the best alternative and evidence from such studies, though imperfect, would be the key evidence sought. Observational epidemiologic studies cannot unequivocally demonstrate causality, but can document associations. In the field of statistics, two variables (e.g., a putative cause and a putative outcome) are said to be associated if and only if they are not independent. Two variables are independent if and only if the conditional distribution of one variable is identical for all levels of the other variable. Associations observed in observational epidemiologic studies are more compelling with respect to possible inference to causation when the study is well designed, conducted, and analyzed. Again, one or more studies finding supportive results are not sufficient to support a claim if they are only a subset of a larger number of studies some of which obtain contradictory evidence and the weight of evidence is not supportive. It is also critically important to distinguish between the concepts of *association* and *co-occurrence*. Co-occurrence, for example a case report where ingestion of a compound occurs in a person who also experiences some event, does not indicate association but is, unfortunately, often mistakenly referred to as evidence of association (See Adams, 2004).

3.3.4. Critically, because randomization is not used in observational epidemiologic studies, potential confounding factors must be delineated, carefully measured, and carefully controlled for in the statistical analysis. Unlike RCTs which can control for both known and unknown confounding factors, observational epidemiologic studies can only control for confounders to the extent that the

confounding variables can be effectively measured and for which the functional form of the relation between the potential confounding variable and the outcome can be effectively modeled in the statistical analysis.

4. The Risks of Obesity and Overweight.

4.1. The clinical and public health problem of overweight and obesity is now well recognized by virtually every major body concerned with public health including the National Institutes of Health (National Task Force on Prevention and Treatment of Obesity, 1994), the Centers for Disease Control (Mokdad et al., 2001; 2004), the United States Department of Agriculture (USDA Center for Nutrition Policy and Promotion, 1998), and the World Health Organization (WHO, 1998). On January 8, 2001, then Surgeon General, David Satcher issued a press release announcing a year-long effort to develop a national action plan for reducing the prevalence of overweight and obesity in the US. Dr. Satcher stated, "The prevalence of overweight and obesity has nearly doubled among children and adolescents since 1980. It is also increasing in both genders and among all population groups of adults. We want to establish strategies and set priorities so that we can successfully implement obesity prevention efforts that focus on the family and community, schools, work sites, the health care delivery system, and the media."[2]

4.2. The evidence that overweight and obesity are highly prevalent (Flegal et al., 1998), economically costly to society (Allison et al., 1999a), increase mortality rate (at least in the case of obesity) (Allison et al., 1999b; Mokdad et al., 2004), reduces quality of life (Fontaine et al., 2000) and increases the risk of various morbidities (Billington et al., 2000) is quite clear. Reports from the CDC show that obesity rates continue to climb (Ogden et al. 2002; Flegal et al., 2002) and the importance of aggressively addressing obesity has been reaffirmed by many government agencies including National Institute of Diabetes Digestive and Kidney Disease (http://www.niddk.nih.gov/welcome/releases/12-13-01.htm). A recent report from my group estimates that extreme obesity can truncate expected lifespan by 5 to 20 years among young adults (Fontaine et al., 2003). A detailed review of the evidence that overweight and obesity cause a wide variety of severe and common deleterious health consequences is beyond the scope of this report, but is extensively documented in a number of publications (e.g., Allison & Pi-Sunyer, 1995; NHLBI, 1998; Pi-Sunyer, 2003; WHO, 1998).

5. The Benefits of Weight Loss Among Obese & Overweight Persons.

5.1. That there are short term benefits of weight loss is clear. These benefits include, but are not limited to:

- Improvements in indicators of glucose tolerance (Goldstein, 1992; NHLBI, 1998).
- Improvements in serum lipid profile (Dattilo & Kris-Etherton, 1992; Hecker et al., 1999; NHLBI, 1998).
- Reductions in blood pressure (Goldstein, 1992; NHLBI, 1998).
- Improvements in respiratory mechanics and daytime oxygenation (Hakala et al., 2000).

2 http://www.surgeongeneral.gov/todo/pressreleases/obesitypressrelease.htm

- Reductions in inflammatory markers (Esposito et al., 2003).

5.2. There are additional short-term benefits beyond those discussed above. These include but are not necessarily limited to, increased quality of life (Fontaine & Barofsky, 2001), improved mood even if weight is regained (Foster et al., 1996), reduced medication costs (Agren et al., 2002), reduced sick leave and disability pension (Narbro et al., 1999), increased income (Naslund & Agren, 1991), and improved sexual functioning (Kolotkin & Crosby, 2002).

5.3. Long-term benefits of weight loss are more difficult to study and less well documented. However, compelling data are beginning to appear. Several years ago, after a review of the literature, Pi-Sunyer (1996) wrote "*Obesity leads to and exacerbates many serious disorders, including hypertension, dyslipidemia, cardiovascular disease, non-insulin-dependent diabetes mellitus, gallbladder disease, respiratory dysfunction, gout, and osteoarthritis. Many short-term studies have shown that weight loss can ameliorate or, in some cases, reverse such disorders. Fewer long-term studies-defined as those whose combined acute intervention and follow-up phases extend for at least 1 year-of the therapeutic benefits of weight loss on specific disorders have been undertaken. Those long-term studies that have been performed tend to confirm the results of briefer studies. Even when weight loss has been comparatively modest or some degree of weight regain has occurred, weight loss is generally associated with a decrease in risk factors and the alleviation of clinical symptoms.*"

5.4. Recently, several key studies have appeared. First, the Swedish Obese Subjects (SOS) study is the largest best controlled trial of surgically induced weight loss conducted to date. Recent data with 8 years of follow-up have been reported (Torgerson & Sjostrom, 2001). The authors found that "*Weight reductions achieved in the surgical group reduced the two-y incidence of diabetes 32 times as compared to the controls. After eight years there was still a 5-fold reduction in diabetes incidence.*"

5.5. Second, results from the NIH-sponsored Diabetes Prevention Program were recently reported (Knowler et al., 2002). This study, which I had the privilege of helping to design (Diabetes Prevention Program Research Group, 1999), assigned over 3,000 people with impaired glucose tolerance to receive placebo, metformin (an anti-diabetes drug), or a lifestyle-modification program intended to produce at least a 7 percent weight loss and followed subjects for up to 4 years. "*The lifestyle intervention reduced the incidence by 58 percent (95 percent confidence interval, 48 to 66 percent) and metformin by 31 percent (95 percent confidence interval, 17 to 43 percent), as compared with placebo; the lifestyle intervention was significantly more effective than metformin.*"

5.6. Third, Torgerson et al. (2004) conducted a 4-year, randomized, double-blind, prospective study, of 3,305 obese non-diabetic patients assigned to lifestyle changes plus either orlistat (a weight loss drug) or placebo. After 4 years of treatment, the cumulative incidence of diabetes was reduced by 37% (P = 0.0032). This occurred despite the fact that the mean weight loss with orlistat was only 2.8 kg above and beyond that produced by placebo. This further emphasizes that modest weight loss can produce important reductions in the development of diabetes among obese persons.

5.7. Fourth, recent epidemiologic data are now showing that trying to lose weight (which may include, but is not limited to, doing so through the use of dietary supplements) and weight loss among obese and overweight persons is associated with statistically significant reductions in mortality rate (Gregg et al., 2003).